REMARKS

In response to the Office Action dated October 5, 2007 and the Advisory Action dated December 28, 2007, Applicant has amended claims 1 and 2 to solely clarify particular aspects of the invention. Support for all the above amendments may be found throughout the specification as originally filed. In particular, for example, at page 5, line 32 to page 6, line 4; page 15, lines 8-9; and **original claim 21**. No new matter has been added. The above amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application. Following the amendments, claims 19-21 are canceled and claims 1-12, 15-18, 25, and 27-28 are under consideration. Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and the following remarks.

New Matter Rejection

The Examiner has rejected claims 1 and 2 for allegedly introducing new matter. Specifically, the Examiner contends that the specification describes a light dose between 500J and 10,000J but does not describe a light dose between 500J/cm2 and 10,000J/cm2. Further, the Examiner contends that the specification does not limit the radiation exposure from 2 hours and 24 hours to a specific dose of light. Applicant respectfully traverses this rejection and submits that the specification provides full written description support for the present claim amendments, and thus, does not constitute new matter. Applicant, without acquiescence, has amended claims 1 and 2 to recite: "wherein the duration of radiation exposure is between about 2 hours and 24 hours, and the total fluence of the light used for irradiating is between 500J/cm2 and 10000J/cm2." Support for these amendments can be found specifically on page 15, lines 8-9 and original claim 21.

Applicant respectively submits that original claim 21 recites: "The method of claim 1 or 2, wherein the **total fluence of the light** used for irradiating is between 500 Joules/ cm2 and 10,000 Joules/cm2." Applicant respectfully submits that the phrase "total light dose" is

equivalent to "total fluence of the light" as evidenced by their use interchangeably throughout the specification.

Furthermore, Applicant has included the same definition of the term "fluence" from two different sources to demonstrate the art accepted equivalence of the terms "fluence" and "light dose" and the inherent parameter of area when speaking about fluence (Bushberg, 2002. The Essential Physics of Medical Imaging: Lippincott Williams & Wilkins; Jayaraman, S. and Lanzl, L. 2004. Clinical Radiotherapy Physics: Springer) (copies of the definitions are provided for your convenience).

Moreover, the specification on page 15, lines 8-9, specifically defines a duration of radiation exposure between about 2 hours and 24 hours. The skilled artisan would interpret this passage to mean that the total fluence of light of 500 J to 10,000 J delivered to a unit area per square centimeter (*e.g.*, original claim 21) could be administered over a time period of 2 to 24 hours. The fact that original claim 21 specifically recites the total fluence of the light to be between 500J/cm2 and 10,000J/cm2 further supports Applicant's argument, and merely serves to limit claims 1 and 2 to an amount of light delivered over a particular area (*i.e.*, a dose) as is commonly known in the art of photodynamic therapy (*see* attached definitions).

Applicant further submits that this amendment describes one unexpected feature of the presently claimed invention, which is the utilization of **low power**, non-coherent light sources for unexpectedly long periods of time (*e.g.*, greater than 2 hours) in order to achieve **higher total light doses** to effectively treat vascular lesions. The objective of such treatment is to minimize collateral tissue damage, and simultaneously maximize the therapeutic potential of the presently claimed invention (page 11, lines 18-24). Moreover, Applicant submits that none of the references cited by the Examiner teach these properties.

Claim rejections under 35 U.S.C. § 103, first rejection

Claims 2, 3, 9-12, 15-21, 25, 27 and 28 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Abels *et al.* (WO 97/31582) in view of the abstract of Goetz *et al.* (WO 97/33620), Schultes *et al.* (SPIE, 1994, Vol. 2078, pp.148-157) and further in view of Theodore *et al.* (WO 95/15979). The Action asserts that Abels *et al.* teach the use of ICG for

treating vascularized tumors and their metastases, comprising administering ICG followed by irradiation with light. Abels *et al.* allegedly teach the light source as recited in claim 3, low fluence rates, and the doses as recited in the instant claims. The Action concedes that Abels *et al.* do not teach conjugation of ICG with targeting antibodies. The Action relies on Schultes *et al.* and the abstract of Goetz *et al.* to overcome this deficiency. Further, the Action asserts that it would have been obvious to the skilled artisan at the time the invention was made to combine the teachings of Theodore *et al.* on pretargeting with the other cited references to arrive at Applicant's invention. As such, the Action alleges that it would have been *prima facie* obvious at the time the invention was made for the skilled artisan to combine the teachings of the cited references to arrive at Applicant's invention.

Applicant respectfully traverses this basis of rejection and submits that none of the references cited by the Examiner alone or together teach or suggest each and every limitation of the claims. Moreover, the main reference cited by the Examiner, Abels *et al.*, teaches away from the novel and unobvious features of the presently claimed invention, namely a prolonged radiation exposure time and higher total light dosage as well as treating lesions in the vascular system, and thus, the Examiner has failed to establish a *prima facie* case of obviousness against the claimed invention.

The Examiner maintains the allegation that Abels *et al.* teach PDT at a substantially lower light intensity than used with photothermal therapy (page 10, lines 11-14 and 18-20). Applicant submits that these passages cited by the Examiner actually teach away from the presently claimed methods, which employ high total light doses, which are considered photothermal by Abels *et al.* Applicant submits that Abels *et al.*, on p. 10, lines 11-14, refer to a "lower light intensity and **lower total light dose** than that employed in Chen *et al.* in *in vitro* photothermal experiments". Moreover, lines 18-20 refer to lower total light dose and not to a lower light intensity (*e.g.*,"**Most preferably, the total light dose is an order of magnitude lower** than that employed for photothermal treatment").

Abels *et al.* further teach away from Applicant's presently claimed ranges of total light dose (see claims 1 and 2; "total fluence of the light used for irradiating is between 500J/cm2 to 10000J/cm2"). Abels *et al.* teach "light doses which generally are effective for phototherapy

but ineffective for photothermal destruction include those of 250J/cm2 or less" (p8, lines 1-3). Further, Abels *et al.* teach "doses greater than 250J/cm2 may be effective for photothermal destruction" (p.8, lines 7-9). Furthermore, Abels *et al.* teach that "It is highly significant that this light dose (10J/cm2 to 200J/cm2) is substantially lower that light doses necessary for photothermal effects, which generally require about ten times the present light dose (i.e., 100J/cm2 to 2000J/cm2). Abels *et al.* **strongly** teach away from Applicant's preferable range of total light dose (500-10000J/cm2), and in contrast, teach that the Applicant's presently claimed total light dose range would be equivalent to photothermal light doses. Applicant submits that the skilled artisan upon reading Abels *et al.*, would equate the claimed ranges of Applicant's total light dose with doses used in damaging photothermal therapy, and not the presently claimed PDT. Thus, the skilled artisan would not have been motivated to use the Applicant's claimed ranges of total fluence of the light used for irradiating between 500J/cm2 and 10000J/cm2, and consequently, would not arrive at the presently claimed invention.

Moreover, Abels *et al.* teach away from Applicant's presently claimed duration of radiation exposure between about 2 hours and 24 hours. Applicant submits that the sole exemplification in Abels *et al.* is an *in vivo* treatment of a lesion not present in the vascular system (*e.g.*, Kaposi's Sarcoma; see below), and teaches an intensity of 3W/cm2, a radiation exposure time of **33 seconds**, and a total light dose of only 100J/cm2. Applicant submits that this example in Ables *et al.* further teaches away from using a preferable total fluence of the light used for irradiating of 500J/cm2 to 10000J/cm2 and a duration of radiation exposure between about 2 hours and 24 hours. Applicant submits that the skilled artisan would further be discouraged from using Applicants claimed ranges for total light dose and duration of radiation exposure to treat lesions of the vascular system, and thus, fail to arrive at the presently claimed invention.

The Examiner also maintains the contention that Abels *et al.* teach a photodynamic method for treating highly vascularized tumors and their metastases, such as Kaposi's sarcoma; adenocarcinoma of the colon, esophagus, breast; neurofibroma and malignant melanoma. Further, the Examiner contends that "Because the tumors are highly vascularized, they are without a doubt within the vascular system". Applicant submits that the Examiner has

erred in redefining the components of the vascular system. Applicant submits that a tissue that is merely capable of inducing angiogenesis is not sufficient to define said tissue as part of the vascular system. The skilled artisan would understand the widely accepted art definition that the vascular system includes blood vessels, namely, arteries, arterioles, veins, venules, and capillaries. Applicant accepts the art established definition of a vascular system, and further submit that this definition cannot be altered to include features that the Examiner deems necessary, and that the skilled artisan would understand that the components of the vascular system are an immutable fact. Moreover, Kaposi's sarcoma is not a lesion of the vascular system, but rather the lymphatic system (Dupin *et al.*, 1999. *PNAS USA*, Vol. 96, pp. 4546-4551; Kahn *et al.*, 2002. *Mod Pathol*, Vol. 15, No.4, pp. 434-440). Applicant further submits that adenocarcinomas are epithelial tumors that are glandular in origin; neurofibromas are of glial origin; melanomas derive from melanocytes; and breast and esophageal cancers arise from their respective tissues, and thus, none of these cancers can be characterized as a lesion in the vascular system. Furthermore, the cancers appropriate for treatment by the method of Abels *et al.* are not lesions within the vascular system. This is crucial since Abels *et al.* actually teach that light therapy is initiated immediately after administration of the dye so that the dye is still in the area to be treated, *i.e.*, the skin and subcutaneous area (*see* for example, Example 2 at page 26 where irradiation of KS lesions begins 1 minute following the last bolus of dye). Therefore, in fact, Abels *et al.* teach away from the present method where "the photosensitizing agent is cleared from the skin and subcutaneous tissues of the subject prior to the irradiation" as presently claimed.

Applicant submits that not only does Abels *et al.* teach away from Applicant's claimed ranges of total fluence of the light used for irradiating and duration of radiation exposure, but the reference also teaches away from using PDT against lesions in the vascular system and wherein the photosensitizing agent is cleared from the skin and subcutaneous tissues of the subject prior to the irradiation . Thus, the skilled artisan, upon reading Abels *et al.*, would not seek to treat lesions in the vascular system with Applicant's unexpected and nonobvious features of a duration of radiation exposure between about 2 hours and 24 hours and a total fluence of the light used for irradiating is between 500J/cm2 and 10000J/cm2.

Applicant submits that neither Schultes *et al.*, Goetz *et al.*, nor Theodore *et al.* alone or in combination is sufficient to overcome the deficiencies of Abels *et al.* Neither of the references teach Applicant's unexpected and unobvious features of a duration of radiation exposure between about 2 hours and 24 hours and a total fluence of the light used for irradiating is between 500J/cm2 and 10000J/cm2 in the presently claimed invention. Schultes *et al.* merely describe the development of a water-soluble antibody-coupled Phthalocyanine and the use of this compound in *in vitro* and rat model settings of ovarian carcinoma and in breast cancer lesions. Schultes *et al.* fail to cure the deficiencies of Abels *et al.,* in particular by providing no actual teaching with regard to the use of targeting conjugates in methods for destroying target cells in lesions of the vascular system. The abstract of Goetz *et al.* also fails to remedy the deficiencies of Abels *et al.* and in fact provides only a single sentence describing the use of ICG-antibody conjugates for the treatment of tumors. Similarly, and as noted previously, Theodore *et al.* only generally teaches the use of a pretargeting approach for localizing photosensitizing agents. Thus, none of these references teaches destroying cells that comprise lesions of the vascular system using the claimed methods wherein a duration of radiation exposure between about 2 hours and 24 hours and a total fluence of the light used for irradiating between 500J/cm2 and 10000J/cm2, particularly in view of the teachings of Abels *et al.* Furthermore, neither of the references teach the targeting agents of Applicant.

Applicant submits that the Examiner has failed to establish a *prima facie* case of obviousness against the presently claimed invention. The main reference relied on by the Examiner, Abels *et al.*, teaches away from Applicant's methods, and thus, the skilled artisan would not seek to use the Applicant's claimed ranges for total light dose, duration of radiation exposure, or even treating lesions in the vascular system. As none of the secondary references compensates for the deficiences of Abels *et al.*, these references fail to teach or suggest every limitation of Applicant's presently claimed methods of PDT, and thus, does not render the presently claimed invention obvious.

Accordingly, in view of the above amendment and remarks, Applicant kindly requests that the Examiner carefully reconsider and withdraw this basis for rejection.

Claim rejections under 35 U.S.C. § 103, second rejection

Claims 1-12, 18-21, 25 and 28 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Abels *et al.* (WO 97/31582) and Schultes *et al.* (SPIE, 1994, Vol. 2078, pp.148-157) in view of Williams *et al.* (US Patent No. 5,576,013), Ruoslahti *et al.* (US Patent No. 6,180,084) and Chen *et al.* (US Patent No. 5,445,608). The Action reiterates the teachings of Abels *et al.* as summarized above and further asserts that Schultes *et al.* teach that administration of the antibody conjugated photosensitizer versus the photosensitizer alone allows for a reduction in the dose of photosensitizer used and the more selective binding to target cells allows for reduced cutaneous phototoxicity. Ruoslahti *et al.* allegedly teach the targeting of cytotoxic agents to angiogenic vasculature of a tumor by means of peptides which bind to the NGR receptor in tumor neovasculature. Williams *et al.* allegedly teach that targeting the blood supply of a lesion is more effective than targeting the lesion itself, and the Action asserts that this is consistent with targeted localization of photosensitizing agents by means of specific ligands which bind to the tumor vasculature. Chen *et al.* allegedly discloses an apparatus comprising a variety of light sources suitable to apply PDT to external surfaces of the body. The Action concludes that it would have been *prima facie* obvious at the time the claimed invention was made to combine the teachings of these references to arrive at Applicant's invention.

Applicant respectfully traverses this basis of rejection and submits that none of the references cited by the Examiner alone or together teach or suggest each and every limitation of the claims. Moreover, as described in the previous rejection Abels *et al.*, teaches away from the novel and unobvious features of the presently claimed invention, namely a prolonged radiation exposure time and higher total light dosage as well as treating lesions in the vascular system. Applicant submits that the secondary references of Williams *et al.*, Ruoslahti *et al.*, and Chen *et al.* fail to remedy the deficiences of Abels *et al.*, and thus, the Examiner has failed to establish a *prima facie* case of obvious against the claimed invention. However, Applicant will address the failings of these secondary references solely for the sake of completeness.

Concerning Ruoslahti *et al.*, this reference merely describes tumor homing molecules that, in certain embodiments, can be fused to cytotoxic agents. Though numerous agents are listed, only doxorubicin is specifically exemplified and no mention is made of

photosensitizing agents as cytotoxic agents nor activation of the photosensitizing agent using irradiation from light sources. There is simply no teaching or suggestion in this reference of using such agents, either targeted or not, for destroying target cells in lesions of the vascular system. Williams *et al.* teach using photosensitizing agents to cut off blood supply to a lesion that is **not present in the vascular system**, thereby causing blood clots in the vessels, and thus, indirectly treating a non-vascular system lesion. As such, the methods of Williams *et al.* would actually destroy vessels of the vascular system, which is precisely the opposite intended therapeutic benefit of the presently claimed invention (p.4, lines 2-5 of the as-filed specification). Applicant submits that this reference actually teaches away from the presently claimed methods and in no way remedies the deficiencies of Abels *et al.*

Chen also does not remedy the deficiencies of Abels *et al.* in that it only teaches an apparatus for delivering light-activated therapy. There is simply no teaching in this reference of the presently claimed methods of administering to the subject a therapeutically effective amount of a photosensitizing agent, wherein the photosensitizing agent is conjugated to a ligand that selectively binds to a receptor on target cells of the lesion in the vascular system or administering to the subject a therapeutically effective amount of a first conjugate comprising a first member of a ligand-receptor binding pair conjugated to an antibody or antibody fragment, wherein the antibody or antibody fragment selectively binds to the target cell that comprises the lesion in the arterial vascular system.

Applicant submits that the Examiner has failed to establish a *prima facie* case of obviousness against the presently claimed invention because the references cited by the Examiner do not teach or suggest every limitation of the claims. Moreover, the secondary references of Schultes *et al.*,Williams *et al.*, Ruoslahti *et al.*, and Chen *et al.* either alone or in combination fail to remedy the insufficiencies of Abels *et al.*, which actually teach away from the presently claimed invention. The skilled artisan would clearly not arrive at the presently claimed invention in view of the references cited by the Examiner, and thus, these references do not render the presently claimed invention obvious.

Accordingly, Applicant respectfully requests that the Examiner carefully consider and withdraw this basis for rejection.

Applicant respectfully submits that all of the claims remaining in the application are now believed to be in condition for allowance. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC

/William T. Christiansen/
William T. Christiansen, Ph.D.
Registration No. 44,614

WTC:MJM:jto

701 Fifth Avenue, Suite 5400
Seattle, Washington 98104
Phone: (206) 622-4900
Fax: (206) 682-6031

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